REMARKS

Claims 43, 47-51, 53 and 55-96 are pending. Claims 47-49 have been amended slightly to make the phrase "length between" consistent in the claims. No new matter has been added.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 43, 47-51, 53 and 55-96 as obvious in view of Wahlestedt et al. (WO 01/25248; "Wahlestedt") taken with Crooke (U.S. Patent No. 5,898,031).

Wahlestedt teaches antisense oligonucleotides having the formula $[X_mY_nX_p]_q$ wherein: X is an oxy-LNA; Y is a non-oxy-LNA (e.g., standard DNA, RNA, thio-LNA, or amino-LNA); each of m and q is an integer between 0 to 30; n is 0, 1, 2 or 3; and q is an integer from 1 to 10.[1] The Examiner argued that since both m and p can be zero, Wahlestedt teaches oligonucleotides having the formula XYXY where X is a sequence of oxy-LNA and Y is a sequence of non-oxy-LNA.[2] The Examiner conceded that Wahlestedt does not "teach sequences in wherein the length of the non-locked nucleotides is 4-20." However, the Examiner argued that because Crooke teaches the use of gapmer oligonucleotides having deoxynucleotide regions of at least 5 nucleotides, it would have been obvious "to modify the oligonucleotides taught by Wahlestedt et al. in order to produce oligonucleotides having a sequence of non-locked nucleotides of 4-20 nucleotides and would further be obvious to modify the oligonucleotides to have both locked and non-locked regions of specific lengths."

Wahlestedt does not disclose oligonucleotides having the formula XYXY

"A prior art reference that discloses a genus still does not inherently disclose all species within that broad category." *Metabolite Laboratories, Inc. v. Laboratory Corporation of*

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[1] There are certain other limitations in the formula that are not relevant to the present analysis, e.g., limitations regarding the value of q multiplied by the sum of m, n and p.

[2] Although the Examiner referred to the pattern "XYXY", Applicants assume the Examiner means the pattern $X_mY_nX_mY_n$. For the purposes of this reply, Applicants adopt the Examiner's approach and use XYXY to refer to the pattern $X_mY_nX_mY_n$.

America Holdings, 370 F.3d 1354 (Fed. Cir. 2005), *cert. dismissed* ___ U.S. ___ (2006). Wahlestedt discloses a generic formula for oligonucleotides having oxy-LNA and non-oxy-LNA. The generic formula encompasses a very large number different oligonucleotides having different patterns of oxy-LNA sequences and non-oxy-LNA sequences. Wahlestedt does not disclose an oligonucleotide having the pattern XYXY, where X represents a sequence of oxy-LNA and Y represents a sequence of non-oxy-LNA. The disclosure of the generic formula $[X_mY_nX_p]_q$ is not a disclosure of all species within the generic formula, e.g., an oligonucleotide having the pattern XYXY, where X represents a sequence of oxy-LNA and Y represents a sequence of non-oxy-LNA.

Only two specific oligonucleotides are disclosed by Wahlestedt. One of the oligonucleotides ("LNA gab-mer") has the pattern XYX and the other ("LNA-mix-mer") has the pattern YXYXYXYXYXY (see page 10). These are just two of the very large number of different oligonucleotides within the general formula disclosed by Wahlestedt. There is nothing in Wahlestedt to suggest the desirability of generating an oligonucleotide having the pattern XYXY, where X represents a sequence of oxy-LNA and Y represents a sequence of non-oxy-LNA. Since Wahlestedt does not teach or suggest an oligonucleotide having the pattern XYXY, where X represents a sequence of oxy-LNA and Y represents a sequence of non-oxy-LNA, the teachings of Wahlstedt, no matter how modified, cannot render the present claims obvious. On this basis alone, the rejection of the pending claims as obvious should be withdrawn.

One skilled in art would not use the teaching of Crooke to modify the oligonucleotides of Wahlstedt

Even if Wahlestedt did teach or suggest an oligonucleotide having the pattern XYXY, where X represents a sequence of oxy-LNA and Y represents a sequence of non-oxy-LNA, which it does not, the cited prior art would not render the present claims obvious because one of ordinary skill in the art would not use the teachings of Crooke to modify the teachings of Wahlestedt. This is because the oligonucleotides of Crooke are designed for an entirely different purpose than the oligonucleotides of Wahlestedt.

The entire purpose of Wahlestedt is to provide oligonucleotides that hybridize to RNA and recruit RNAase H to cleave the RNA. As Wahlestedt explains, RNAase H binds to DNA/RNA duplexes and does not bind to DNA/DNA duplexes or DNA/RNA duplexes (page 2) However, as Wahlestedt also explains, since DNA has relatively poor nuclease resistance and modest affinity for RNA, great effort has been made to design antisense molecules with the ability to recruit RNAse H and while retaining RNA binding affinity and leading to the use of molecules that include a stretch of DNA or phosphorothioates (page 2).

Wahlestedt addresses the challenge of creating oligonucleotides that have high affinity for RNA yet recruit RNAase H by employing oxy-LNA. Wahlestedt reports that when oxy-LNA are used in an oligonucleotide, "the activity of RNAse H is not contingent on a contiguous stretch of DNA or phosphorothioate bases" (page 3). In fact, Wahlestedt report that "oligonucleotides composed entirely of oxy-LNA are able to recruit RNAase H" (page 3).

Crooke has an completely different focus – the design of oligonucleotides that will hybridize to RNA forming "double-stranded RNA like structures" that can be cleaved by "double-stranded RNase enzymes" (column 8, lines 43-60). Thus, Crooke is concerned with the design of oligonucleotides that recruit dsRNAse, an enzyme that cleaves RNA/RNA duplexes, not DNA/RNA duplexes, which are cleaved by RNAase H. Indeed, Crooke repeatedly emphasizes that his antisense oligonucleotides, which recruit dsRNAse differ from conventional antisense molecules that recruit RNase H (see column 9, lines 17-44). Given that that the oligonucleotides of Wahlestedt are designed to work by a completely different mechanism (RNAase H cleavage) than those of Crooke (dsRNAse cleavage), one skilled in the art would not turn to Crooke to modify the oligonucleotides of Wahlestedt.

If one were to turn to Crooke to modify Wahlestedt, as suggested by the Examiner, the modification would be inconsistent with the goals of Wahlestedt. The Examiner states that Crooke (Example 22, columns 48 and 49) "tests several sequences of gapmers and that the best performing sequences have deoxynucleotide regions of 5 nucleotides." It appears that the Examiner has misread Example 22. In fact, Crooke states that it is optimal to include a region five contiguous ribonucleotides -- not five contiguous deoxyribonucleotides. This is consistent

with Crooke's teaching that useful oligonucleotides include a "first segment" that "incorporates at least one ribonucleoside subunit that is modified to improve at least one of its pharmacokinetic properties, its binding characteristics to target RNA, or to modify its charge" and a "second segment" that "includes at least four consecutive ribofuranosyl nucleoside subunits" (column 4, lines 9-15). In some cases, Crooke explains, the segment of consecutive ribofuranosyl nucleoside subunits (gap) is flanked by segments of modified ribonucleosides (column 9, lines 35-44). Since Wahlestedt teaches that RNA/RNA duplexes cannot be cleaved by RNAase H, one seeking to modify Wahlestedt would avoid the teaching in Crooke, highlighted by the Examiner, regarding incorporating at least five contiguous ribonucleotides that is.

There is a second, independent reason that one seeking to modify Wahlestedt would not turn to Crooke. Wahlestedt concerns oligonucleotides that incorporating oxy-LNAs and the advantages provided by incorporating oxy-LNAs. However, there is no mention of LNA, much less oxy-LNA in Crooke. Given this, even if Wahlestedt disclosed oligonucleotides having the pattern XYXY, which it does not, one skilled in the art would not turn to Crooke for suggestions on how to optimize the number of nucleotides in the various portions of the oxy-LNA containing oligonucleotides of Wahlestedt.

In view of the forgoing, Applicant respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

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